

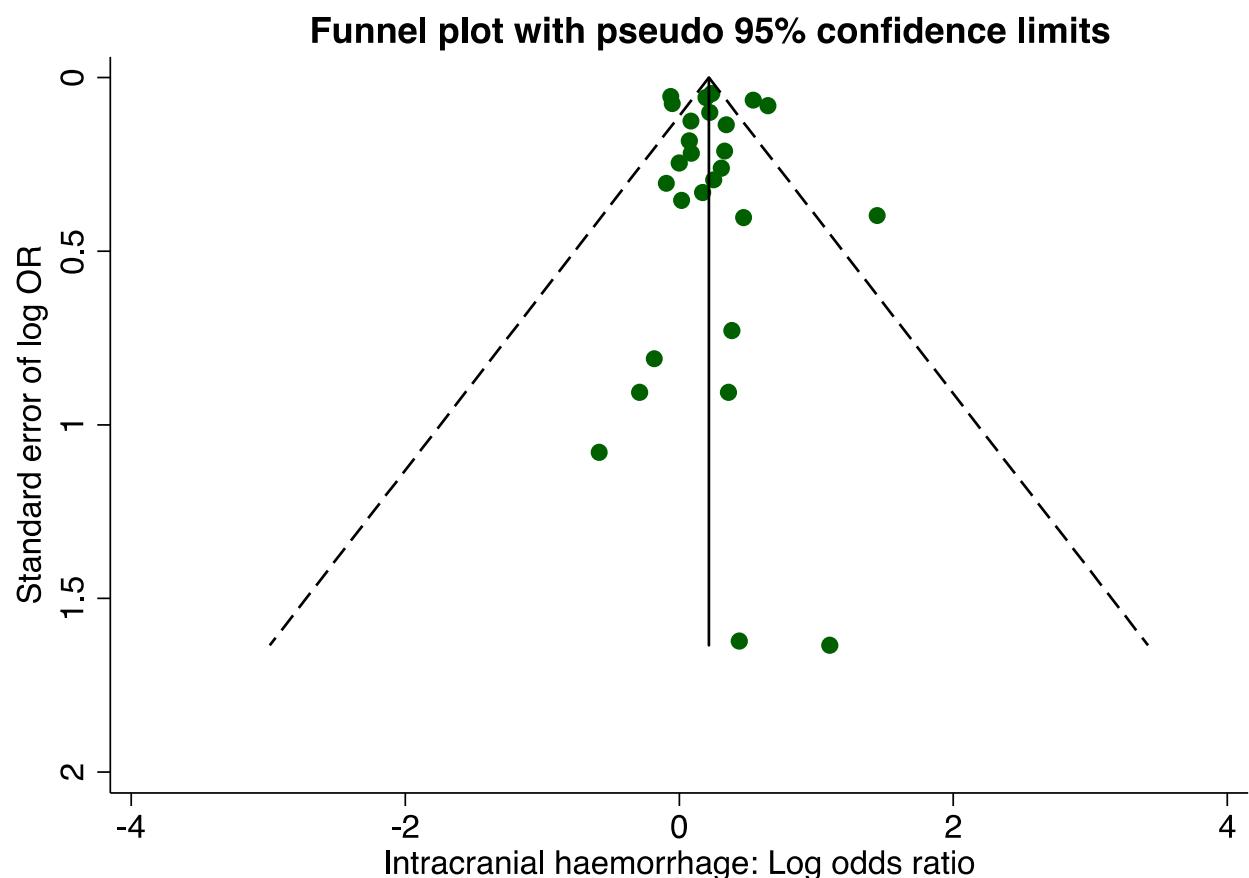
The impact of selective serotonin reuptake inhibitors on the risk of intracranial haemorrhage: A systematic review and meta-analysis

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Appendix

<i>Online Figure 1: Funnel plot for intracranial haemorrhage</i>	2
<i>Online Figure 2: Sensitivity analysis by the definition of the bleeding event used</i>	3
<i>Online Table 1: Search strategy</i>	5
<i>Online Table 2: Description of studies</i>	7
<i>Online Table 3: Detailed characteristics of studies</i>	10
<i>Online Table 4: Risk of Bias Assessment (Observational Studies)</i>	12
<i>Online Table 5: Risk of Bias Assessment (Randomised Controlled Trials)</i>	14
<i>References for appendix</i>	15

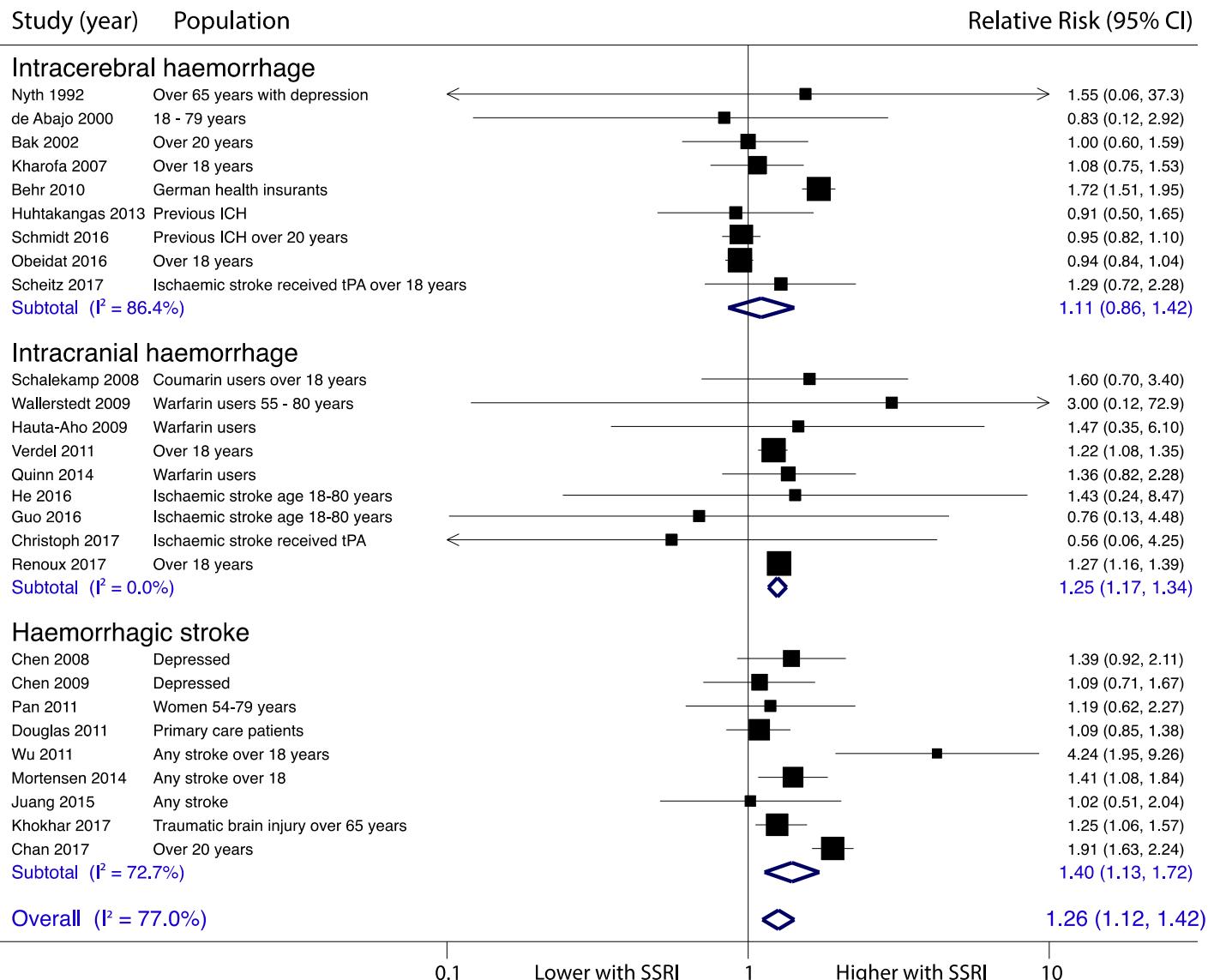
Online Figure 1: Funnel plot for intracranial haemorrhage



Each circle represents a particular study. Dotted lines represent the pseudo 95% confidence intervals.
ICH: Egger p = 0.82, Begg p = 0.68.

Online Figure 2: Sensitivity analysis by the definition of the bleeding event used

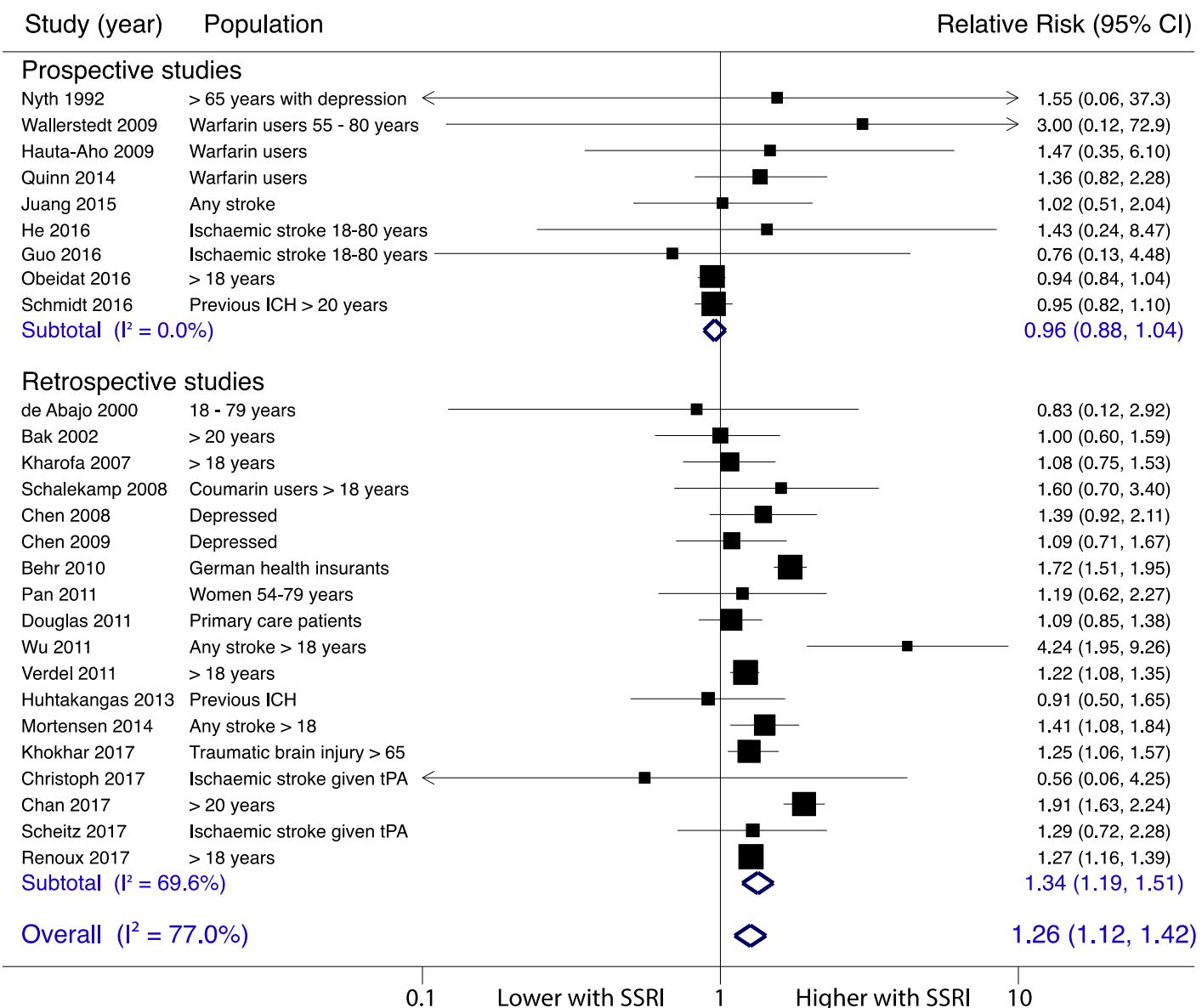
Intracranial Haemorrhage by bleeding definition



Forest plot is sub-grouped by the definition used of the bleeding event. The diamond represents the pooled difference using a random-effects model. I^2 is the percentage of total variation across studies due to heterogeneity.

Online Figure 3: Sensitivity analysis by study design

Intracranial Haemorrhage by study design



Forest plot is sub-grouped according prospective and retrospective study designs. The diamond represents the pooled difference using a random-effects model. I^2 is the percentage of total variation across studies due to heterogeneity.

Online Table 1: Search strategy

Database	MESH terms
Cochrane	1. serotonin uptake inhibitor*:ti,ab,kw 2. "selective serotonin reuptake inhibitor":ti,ab,kw or "selective serotonin reuptake inhibitors":ti,ab,kw 3. "specific serotonin reuptake inhibitor":ti,ab,kw or "specific serotonin reuptake inhibitors":ti,ab,kw 4. SSRI:ti,ab,kw or SSRIs:ti,ab,kw 5. amoxapine or citalopram or fenfluramine or fluoxetine or fluvoxamine or norfenfluramine or paroxetine or sertraline or trazodone or vilazodone hydrochloride or zimeldine or escitalopram:ti,ab,kw 6. #1 or #2 or #3 or #4 or #5 7. *cerebr* haemorrhag* or *cerebr* hemorrhag* 8. stroke 9. cerebrovascular accident 10. (brain* or cerebr* or cerebell* or intracerebral or intracran*) near/5 (haemorrhag* or hemorrhag*):ti,ab,kw 11. #7 or #8 or #9 or #10 12. #6 and #11
MEDLINE	1. exp Serotonin Uptake Inhibitors/ 2. selective serotonin reuptake inhibitor*.mp. 3. specific serotonin reuptake inhibitor*.mp. 4. SSRI*.mp. 5. amoxapine.mp. 6. citalopram.mp. 7. fenfluramine.mp. 8. fluoxetine.mp. 9. fluvoxamine.mp. 10. norfenfluramine.mp. 11. paroxetine.mp. 12. sertraline.mp. 13. trazodone.mp. 14. vilazodone hydrochloride.mp. 15. zimeldine.mp. 16. escitalopram.mp. 17. exp Intracranial Hemorrhages/ 18. exp Cerebral Hemorrhage/ 19. stroke.mp. 20. ((brain* or cerebr* or cerebell* or intracerebral or intracran*) adj5 (haemorrhag* or hemorrhag*)).mp. 21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 22. 17 or 18 or 19 or 21 23. 21 and 22 24. limit 23 to yr="1980-current"
Embase	1. exp serotonin uptake inhibitor/ 2. selective serotonin reuptake inhibitor*.mp. 3. specific serotonin reuptake inhibitor*.mp. 4. SSRI*.mp. 5. amoxapine.mp. 6. citalopram.mp.

Database	MESH terms
	<p>7. fenfluramine.mp. 8. fluoxetine.mp. 9. fluvoxamine.mp. 10. norfenfluramine.mp. 11. paroxetine.mp. 12. sertraline.mp. 13. trazodone.mp. 14. vilazodone hydrochloride.mp. 15. zimeldine.mp. 16. escitalopram.mp. 17. exp brain haemorrhage/ 18. exp cerebrovascular accident/ 19. stroke.mp. 20. ((brain* or cerebr* or cerebell* or intracerebral or intracran*) adj5 (haemorrhag* or hemorrhag*)).mp. 21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 22. 17 or 18 or 19 or 20 23. 21 or 22</p>

Online Table 2: Description of studies

Study	Design	Population	Setting	SSRI n	Control n	Mean follow-up duration (months)
Outcome: First-ever ICH						
Nyth 1992 ¹	Prospective	Adults with depression, aged over 65	7 centre study in Denmark, Norway, and Sweden	88	45	1.5
de Abajo 2000 ²	Retrospective	Healthy adults, aged 18-97	GPRD (GP database), UK	12	95	47
Bak 2002 ³	Retrospective	Healthy adults, aged over 20	Funen County registry (civil registry), Denmark	763	38664	36
Kharofa 2007 ⁴	Retrospective	Healthy adults, aged over 18	GERFHS (patient and control database), USA	202	2074	23
Chen 2008 ⁵	Retrospective	Adults with depression, age criteria not specified	PHARMetrics database (medical claimants), USA	141	491	30
Schalekamp 2008 ⁶	Retrospective	Coumarin users, aged over 18	PHARMO Record Linkage System (pharmacy database), Holland	n/s	n/s	84
Chen 2009 ⁷	Retrospective	Adults with depression, age criteria not specified	PHARMetrics database (medical claimants), USA	182	362	30
Hauta-Aho 2009 ⁸	Prospective	Warfarin users, age criteria not specified	Turku University Hospital (hospital database), Finland	828	3614	102
Smoller 2009* ⁹	Prospective	Healthy post-menopausal women, aged 50-79	Women's Health Initiative (3 longitudinal cohorts), USA	3040	130797	70.8
Wallerstedt 2009 ¹⁰	Prospective	Warfarin users, aged 55-80	Centre of Coagulation Sahlgrenska University Hospital (hospital database), Sweden	117	117	40.5
Behr 2010 ¹¹	Retrospective	Health insurants, age criteria not specified	Pharmacoepidemiological Research Database (medical claimants), Germany	1282	88229	26.6
Douglas 2011 ¹²	Retrospective	Primary care patients, age criteria not specified	GPRD (GP database), UK	488	1500	54
Pan 2011 ¹³	Retrospective	Healthy women, aged 30-55	Nurses' Health Study Cohort	n/s	n/s	72

Study	Design	Population	Setting	SSRI n	Control n	Mean follow-up duration (months)
<i>Outcome: First-ever ICH</i>						
			(longitudinal cohort), USA			
Verdel 2011 ¹⁴	Retrospective	Healthy adults, aged over 18	PHARMO Records Linkage System (pharmacy database), Holland	419	14348	60
Wu 2011 ¹⁵	Retrospective	Healthy adults, aged over 18	National Health Insurance Research Database (insurance database), Taiwan	n/s	n/s	66
Hung 2013* ¹⁶	Retrospective	Healthy adults, aged over 65	National Health Insurance Research Database (insurance database), Taiwan	n/s	n/s	54
Mortensen 2013* ¹⁷	Prospective	Ischaemic stroke survivors, aged over 18	Stroke Registry (patient database), Denmark	n/s	n/s	38.6
Huhtakangas 2013 ¹⁸	Retrospective	ICH survivors, age criteria not specified	Oulu University Hospital stroke registry (patient database), Finland	185	421	43.5
Quinn 2014 ¹⁹	Prospective	Warfarin users, age criteria not specified	ATRIA (database of patients with atrial fibrillation), USA	1743	7443	42
Mortensen 2014 ²⁰	Retrospective	Stroke survivors, aged over 18	Danish Stroke Registry (patient database), Denmark	626	626	1
Juang 2015 ²¹	Prospective	Stroke survivors, age criteria not specified	National Health Insurance Research Database (insurance database), Taiwan	661	12075	45.6
Guo 2016 ²²	Prospective	Ischaemic stroke survivors, aged 18-80	The Shenzhen People's Hospital, Shenzhen, China	177	90	6
He 2016 ²³	Prospective	Ischaemic stroke survivors, aged 18-80	The Shenzhen People's Hospital, Shenzhen, China	179	171	6
Obeidat 2016 ²⁴	Prospective	Healthy adults, aged over 18	GERFHS and ERICH (case-control databases), USA	722	8357	31
Schmidt 2016 ²⁵	Prospective	Previous ICH, aged over 20	Danish Civil Registration	3952	3952	96

Study	Design	Population	Setting	SSRI n	Control n	Mean follow-up duration (months)
<i>Outcome: First-ever ICH</i>						
Chan 2017 ²⁶	Retrospective	Healthy adults, aged over 20	System (civil registry), Denmark National Health Insurance Research Database (insurance database), Taiwan	16543	396942	390
Schellen 2018 ²⁷	Retrospective	Ischaemic stroke survivors who received tPA, age criteria not specified	VISTA (trials archive database), UK	135	979	0.05
Khokhar 2017 ²⁸	Retrospective	Traumatic brain injury survivors, aged over 65	Centres for Medicare & Medicaid Services CCW (insurance database), USA	13827	43355	21.8
Renoux 2017 ²⁹	Retrospective	Healthy adults, aged over 18	UK Clinical Practice Research Datalink, UK	13929	67064	69.6
Scheitz 2017 ³⁰	Retrospective	Ischaemic stroke survivors receiving tPA, aged over 18	TRISP (cohort of ischaemic stroke patients receiving thrombolysis), Europe	266	5976	0.06
<i>Outcome: recurrent ICH</i>						
Huhtakangas 2013 ¹⁸	Retrospective	ICH survivors, age criteria not specified	Oulu University Hospital stroke registry (patient database), Finland	185	421	43.5
Juang 2015 ²¹	Prospective	Stroke survivors, age criteria not specified	National Health Insurance Research Database (insurance database), Taiwan	661	12075	45.6
Schmidt 2016 ²⁵	Prospective	Previous ICH, aged over 20	Danish Civil Registration System (civil registry), Denmark	3952	3952	96

* Study not included in meta-analysis. ATRIA, AnTicoagulation and Risk factors in Atrial Fibrillation; CCW, Chronic Condition Data Warehouse; ERICH, Ethnic/Racial Variations in ICH; GERFHS, Genetic and Environmental Risk Factors for Hemorrhagic Stroke; GPRD, General Practice Research Database; ICH intracerebral haemorrhage; tPA, tissue plasminogen activator; TRISP, Thrombolysis in Ischemic Stroke Patients; UK, United Kingdom; USA, United States of America; VISTA, Virtual International Stroke Trials Archive; n/s not specified.

Online Table 3: Detailed characteristics of studies

Study	Age		Male %		Smoker %		Diabetes %		Hypertension %		Statin %		Heavy alcohol %		CAD %		Anti-coagulant %		Anti-platelet %		NSAID %		Depression %		AF %	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Nyth 1992 ¹	76.1	77.7	33.0	26.7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	100	100	n/a	n/a
de Abajo 2000 ²	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	0	0	0	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Bak 2002 ³	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Kharofa 2007 ⁴	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Chen 2008 ⁵	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	100	100	n/s	n/s
Schalekamp 2008 ⁶	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	100	100	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Chen 2009 ⁷	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	100	100	n/s	n/s
Hauta-Aho 2009 ⁸	69	66	47	54	n/s	n/s	n/s	n/s	36.9	30.7	n/s	n/s	n/s	n/s	100	100	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Smoller 2009* ⁹	63	64	0	0	7.24	6.37	5.3	3.83	n/s	n/s	16.1	12.6	10.8	12	3.8	2.4	n/s	24.5	22.3	24.6	17.9	25.4	8.3	100	100	
Wallerstedt 2009 ¹⁰	72	72	48	48	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	100	100	28	39	26	27	n/s	n/s	n/s	n/s	n/s	n/s
Behr 2010 ¹¹	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Douglas 2011 ¹²	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Pan 2011 ¹³	n/s	n/s	0	0	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Verdel 2011 ¹⁴	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Wu 2011 ¹⁵	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Hung 2013* ¹⁶	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Mortensen 2013* ¹⁷	71.5	71.8	52	51	36.8	36.8	n/s	n/s	53.4	53.3	19.8	20.1	7.5	7.8	n/s	n/s	8.6	8.8	39.1	39.7	n/s	n/s	n/s	n/s	16.9	17.2
Huhtakangas 2013 ¹⁸	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Quinn 2014 ¹⁹	n/s	n/s	47.3	59.3	n/s	n/s	n/s	n/s	50.8	50	n/s	n/s	n/s	n/s	36.8	32.5	100	100	n/s	n/s	n/s	n/s	n/s	n/s	100	100

Study	Age		Male %		Smoker %		Diabetes %		Hypertension %		Statin %		Heavy alcohol %		CAD %		Anti-coagulant %		Anti-platelet %		NSAID %		Depression %		AF %	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Mortensen 2014 ²⁰	76.1	76.3	37.4	35.1	41.4	41.7	15	14.9	89.7	88.8	14.4	16.3	6.7	6.2	9.4	9.3	9.7	7.8	34.8	38.3	n/s	n/s	n/s	n/s	14.5	14.5
Juang 2015 ²¹	n/s	n/s	56.4	60.2	n/s	n/s	37.8	34.1	n/s	n/s	n/s	n/s	n/s	n/s	22.7	21	2.8	3.3	66.7	60	84.6	77.5	8.5	1.5	6.4	7.7
Guo 2016 ²²	60	61	72.3	73.3	16.9	20	31.1	21.1	74.0	73.3	n/a	n/a	9.0	7.0	50.3	42.2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4.5	2
He 2016 ²³	60.5	62.7	72.1	70.2	33.5	29.2	30.7	37.4	74.3	76	n/a	n/a	3.9	6.4	49.7	47.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Obeidat 2016 ²⁴	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Schmidt 2016 ²⁵	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Chan 2017 ²⁶	n/s	n/s	38.3	54.2	n/s	n/s	8.79	2.42	25.4	6.3	n/s	n/s	n/s	n/s	11.6	1.6	2.2	0.2	12.7	3.7	75.8	54.6	n/s	n/s	1	0.1
Schellen 2018 ²⁷	69	72	36.3	60.6	n/s	n/s	25	26	75.8	81.9	35.6	51.7	n/s	n/s	37.7	47.5	n/s	n/s	41.5	81.8	n/s	n/s	n/s	n/s	25	31.6
Khokhar 2017 ²⁸	83	83	36	42	n/s	n/s	42.5	38.9	90.6	87.6	n/s	n/s	3.1	2.2	8.3	8	26.8	23.9	n/s	n/s	n/s	n/s	40.3	17.2	27.8	27
Renoux 2017 ²⁹	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Scheitz 2017 ³⁰	74	70	38.3	56.9	n/s	n/s	21.1	17.1	72.6	66.2	29.8	27.2	n/s	n/s	n/s	n/s	4.9	3.7	43.2	35.9	n/s	n/s	n/s	n/s	28	27.1

* Study not included in meta-analysis. S, SSRI cohort; C, control cohort; n/s not specified.

Online Table 4: Risk of Bias Assessment (Observational Studies)

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective reporting
de Abajo <i>et al.</i> (2000)	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear
Bak <i>et al.</i> (2002)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Kharofa <i>et al.</i> (2007)	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Chen <i>et al.</i> (2008)	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Schalekamp <i>et al.</i> (2008)	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Chen <i>et al.</i> (2009)	Low risk	Low risk	Low risk	High risk	Unclear	Unclear
Hauta-Aho <i>et al.</i> (2009)	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Smoller <i>et al.</i> (2009)*	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Wallerstedt <i>et al.</i> (2009)	Low risk	High risk	Unclear	High risk	Unclear	Unclear
Behr <i>et al.</i> (2010)	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Douglas <i>et al.</i> (2011)	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear
Pan <i>et al.</i> (2011)	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Verdel <i>et al.</i> (2011)	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Wu <i>et al.</i> (2011)	Low risk	Low risk	Low risk	High risk	Unclear	Unclear
Hung <i>et al.</i> (2013)*	Unclear	High risk	Unclear	High risk	Unclear	Unclear
Mortensen <i>et al.</i> (2013)*	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Huhtakangas <i>et al.</i> (2013)	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Quinn <i>et al.</i> (2014)	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Mortensen <i>et al.</i> (2014)	Unclear	Low risk	Low risk	High risk	High risk	Low risk
Juang <i>et al.</i> (2015)	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective reporting
Obeidat <i>et al.</i> (2016)	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk
Schmidt <i>et al.</i> (2016)	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Chan <i>et al.</i> (2017)	Low risk	High risk	Unclear	Unclear	Low risk	Unclear
Schellen <i>et al.</i> (2018)	Low risk	Low risk	Low risk	High risk	Low risk	Unclear
Khokhar <i>et al.</i> (2017)	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Renoux <i>et al.</i> (2017)	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Scheitz <i>et al.</i> (2017)	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear

Risk of bias reported for each domain using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS).

Online Table 5: Risk of Bias Assessment (Randomised Controlled Trials)

Study	Random sequence generation	Allocation concealment	Selective reporting	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data
Nyth <i>et al.</i> (1992)	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Guo <i>et al.</i> (2016)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
He <i>et al.</i> (2016)	Low risk	Low risk	Low risk	High risk	Unclear	Low risk

Risk of bias reported for each domain using the Cochrane Collaboration's tool for assessing risk of bias.

References for appendix

1. Nyth AL, Gottfries CG, Lyby K, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. *Acta Psychiatr Scand* 1992; 86: 138-145. 1992/08/01.
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